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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/961,443	10/30/1997	TIM M. TOWNES	04005/013003	7598

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NEEDLE & ROSENBERG P C  
127 PEACHTREE STREET N E  
ATLANTA, GA 30303-1811

EXAMINER
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CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/10/2003

32

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

08/961,443

Applicant(s)

TOWNES ET AL.

Examiner

Deborah Crouch, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 09 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 and 21-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 October 1997 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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Applicant's arguments filed December 9, 2002 in paper no. 31 have been fully considered but they are not persuasive. The Townes Declarations have been considered to the extent they are discussed. However, they are not found persuasive for the reasons given below. Claims 1-24 are pending. Claims 1-19 and 21-24 are examined in this office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 and 21-24 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "transgenic mouse whose genome comprises a human LCR - hemoglobin switching DNA construct, wherein said genome is further homozygous for murine - and - globin knockout alleles such that said knockout alleles result in said mouse failing to synthesize murine hemoglobin, and wherein said hemoglobin switching construct is expressed such said mouse develops hemolytic anemia", does not reasonably provide enablement for a transgenic nonhuman mammal comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said nonhuman mammal for reasons presented in the office action mailed June 4, 2002 in paper no. 29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues that the examiner is incorrect in the finding that the specification is not enabled for making non-mouse models. Applicant argues that the art at the time of filing enabled nuclear transfer of modified cells. Applicant argues that Campbell (1996) and Campbell (1994), while not specifically discussing nuclear transfer in the production of transgenic mammals, that such is implied in each reference. Applicant argues that the statements made by both Campbell references would lead the skilled

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artisan to know that the references included transgenic animals. Applicant argues that the first sentence in Campbell 1996 states that cloning were grant innumerable advantages to animal biotechnology, and that this statement includes genetically modified cells could be used in nuclear transfer procedures to produce transgenic nonhuman animals. Applicant argues that from the first experiments performed by Sedivy in the mid-1980's, it was understood that blastocyst formation from cultured cells was beneficial for use in transgenesis and specifically in knockout technology. Applicant argues that Seamark (1994) discusses making transgenic animals by nuclear transfer. Applicant argues that it was widely understood at the time of Campbell (1994) and (1996) that transgenic animals were facilitated by the use of both ES cells and nuclear transfer. Applicant continues that the field of transgenesis was especially mature in the field of erythrocyte transgene expression. Applicant argues that the examiner has provided no evidence that indicates that transgenesis would alter the methods of nuclear transfer. Applicant argues that the methods of nuclear transfer of nontransgenic and transgenic cells are not appreciably different. Applicant argues that Pennisi supports this line of argument, where in quoting Campbell, Pennisi states that not much work was needed to add new DNA to cultured fetal cells, select those with the new gene and produce a cloned transgenic animal such as "Polly." Applicant argues that Pennisi also states that the 1999 success of David Ayares in showing that knockout technology could be practiced with nuclear transfer technology, essentially as described in Campbell 1996. Applicant argues that all they need to show was that a method, which works, exist at the time of the priority application, not that the method was shown to work in all of its manifestations at the time of the priority application. Applicant argues that both Campbell references, the art relied on by the PTO and the Townes Declarations I and II indicate that which was enabling at the time of the priority application remains enabling today. Applicant argues that their invention lies not in the making of the knockout animals but that the animal lives on another animal's hemoglobin. Applicant argue that their pioneering work could be practiced as disclosed in the specification for any mammalian species. These arguments are not persuasive.

The simple fact is that references Campbell (1994) and (1996) do not state anything about using nuclear transfer to produce transgenic mammals. It is difficult of analyze the thinking or belief of the

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authors. The examiner is not in a position to know what was meant in a global sense by either of these references. The only thing available to the examiner are the words in the references.

Sedivy is not of record, and thus a comment on its teachings cannot be made. As for Seamark, the reference refers to demonstrated totipotency in the production of cloned non-transgenic cattle (Mullins, page S38, col. 1, lines 9-13). Sheep and cow chimera had been produced, but there is no discussion as to which tissue tissues were from the nuclear donor. Applicant's invention would require that the resultant mammal's bone marrow to contain the globin gene construct. There are no guidelines in the specification or in either Campbell or Seamark to predictably make chimera that expressed the globin transgenic in the appropriate tissue. The only pertinent comment made by Seamark regarding nuclear transfer, is that it is potentially very useful in the production of clonal offspring, and nuclear transfer would eliminate the need for a chimeric generation.

The comment that Pennisi attributes to Campbell refers to the insertion of a single DNA sequence to produce a transgenic mammal. The claims presently being examined require the mammal to lack expression of its native globin sequences, and contain and express a human globin sequence. Thus, the somatic cell to be used in a nuclear transfer procedure would need to undergo two to three separate genetic modifications, some with selection. It is this multiple genetic modification methodology that the art found unpredictable at the time of filing. Pennisi supports this lack of enablement by stating that gene targeting had only worked in mice, and in one experiment in human connective tissue cells, but not in livestock cells (Pennisi, page 1723, col. 3, lines 10-16). Pennisi further states the problem for gene targeting, disruption/insertion of a target gene by homologous recombination, is finding a way to insert the gene before the donor cells become too old, cannot divide, and thus cannot undergo additional modification event (Pennisi, page 1723, col. 3, parag. 1, lines 5-16). Pennisi does state that in 1999, Ayares disclosed two sheep produced two cloned sheep (Pennisi, page 1723, col. 4, parag. 2). However, 1999 is three years after applicant's priority date, much too late to support enablement at the time of filing, and Pennisi does not disclose how the sheep were made, that is there is no description of the cell types, the vectors, or culture conditions, for example, that enabled Ayares to be successful where other

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had not been and overcome art recognized unpredictabilities for homologous recombination in somatic cells such that the cells can be targeted more than once, and remain capable of nuclear transfer. Pennisi states that the work will be published in Nature, but the examiner never found such a publication. The specification does not provide any guidance on the production of the claimed mammals using nuclear transfer coupled with knock out technology so that the targeted cells are able to undergo subsequent routines of targeting and selection.

Whether or not nuclear transfer itself affects transgenesis is not particularly relevant as the art clearly states at the time of filing, that producing the transgenic and/or knock out cells to serve as nuclear donors was unpredictable. At the time of filing, it was unpredictable for the skilled artisan to obtain the starting material for nuclear transfer, the nucleus.

Applicant argues that the references of Campbell (1994) and 1996 disclose methodology for the cloning by nuclear transfer of sheep, cattle, mice and goats. Applicant argues that Polejaeva states that the methodology used was similar, diploid donor nuclei transplanted into MII oocytes that are activated on or after transfer. Applicant argues that Westhusin states that sheep, cattle, goats, pigs and mice have now been produced. Pennisi, it is argued, states that cloning has become "almost common placed." Applicant argues that the teachings of Westhusin, Pennisi and Polejaeva support applicant's assertion as put forth in Townes Declaration I, that methods and knowledge to produce the claimed subject matter were known in the art at the time of filing. These arguments are not persuasive.

Neither Westhusin, Pennisi nor Polejaeva provide guidance on performing multiple genetic modifications in somatic cells, and then performing nuclear transfer. As the art has stated, and summarized above, this was a major unpredictability at the time of filing.

Applicant has performed a Wands analysis to show that the claimed invention was enabled at the time of filing for production of the mammals by nuclear transfer. This argument is not persuasive as the art stated the unpredictability in producing somatic cells with multiple genetic modifications. As the specification does not address this unpredictability, the Wands analysis, which does not take this into consideration, is flawed.

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With regards to the finding of a lack of enablement based on ES cell gene targeting technology, applicant argues that they are not required to show that putative cell lines known at the time of filing were in fact totipotent. Applicant argues that the cells were called totipotent because they had not been shown to be totipotent, but not because the cells were thought not to be totipotent. Applicant argues that the claims don't require the animal to be produced by germ line transmission. Applicant argues that it is undisputed that today ES cells exist for animals such as humans. Applicant argues that the allowance of human ES cells and primate ES cells in US Patents 6,200,806 and 5,843,780 without evidence of germ line transmission indicates that such is not necessary. These arguments are not persuasive.

While there certainly is no requirement for applicant to show that any ES cell is totipotent, to obtain the scope of the present claims, applicant must overcome the evidence presented by the examiner that totipotent ES cells, as evidenced by germ line transmission, were not enabled by the art at the time of filing. Each of the references cited states this. Applicant has not shown in any fashion that these teachings were in adequate. The patents directed to human ES cells and primate ES cells are not relevant. They do not reflect the art at the earliest priority date, whereas Moreadith, Seamark and Mullins do. Further, a reading of the issued claims, indicates that in neither set is totipotency required. It is only totipotent cells, cells that are required for the production of ES cell knock out mammals, that germ line transmission is required. Further, the claims in '806 state "pluripotent" cells. These cells are not useful for producing knock out mammals as the only contribute to some cell types, but not all.

Applicant is correct that for a product, only one method of producing the product need be enabled. However, neither nuclear transfer or ES cell technologies were enabled at the time of filing for other than the indicated scope.

The examiner withdraws the requirement for switching.

The claims are free of the prior art.

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**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Deborah Reynolds, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Zeta Jones, whose telephone number is (703) 305-3291.

The fax number is 703-872-9306.

Dr. D. Crouch  
Friday, March 07, 2003

*Deborah Crouch*  
DEBORAH CROUCH  
PRIMARY EXAMINER  
GROUP 1800-1632